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Editorial

Fibrin opens the “gate” for leukocytes in the endothelium

Migration of blood leukocytes through the layer of endothelial cells into extravascular sites of inflammation is essential for host defense and elimination of the consequences of tissue damage. The transendothelial migration of leukocytes has been shown to be promoted and mediated by various cell adhesion receptors, such as selectins, ICAM-1, and integrins, as well as by multiple chemoattractant molecules [1–4]. Although many aspects of leukocyte transmigration have been studied, some mechanisms, including a link between thrombosis and the recruitment of leukocytes to sites of inflammation, remain not fully elucidated. In this issue of *Thrombosis Research*, an article by Yakovlev and Medved [5] has partially filled this gap by clarifying the molecular basis for the previously discovered novel mechanism of leukocyte transmigration promoted by the interaction of fibrin with the very low density lipoprotein receptor (VLDLR) [6].

The role of fibrin(ogen) and its derivatives in inflammation, including leukocyte transmigration, has been a matter of intensive investigations for decades. Fibrinogen is one of the acute phase proteins up-regulated in response to injury and inflammation, followed by an up to ten-fold increase in its concentration in blood [7]. Both fibrinogen and fibrin are involved in antimicrobial host protection, inflammatory reactions, wound healing, and related pathophysiological processes [8–11]. Despite numerous data that point to a prominent role of fibrin(ogen) in inflammation, the molecular mechanisms of fibrin(ogen)-mediated leukocyte transmigration remain unclear. So far, three main concepts have been put forward to explain the role of fibrin(ogen) in leukocyte transmigration, two of which are based on the physical bridging of leukocytes to the endothelium. First, it was proposed that fibrinogen links leukocytes to the endothelium through its interaction with the leukocyte receptor Mac-1 and endothelial cell receptor ICAM-1, and that such bridging promotes transendothelial migration of leukocytes [12,13]. This mechanism has been questioned because of the fact that soluble fibrinogen is non-reactive with Mac-1, as discussed in the article by Yakovlev and Medved [5]. However, the binding specificity of surface-adsorbed fibrinogen may be distinct from that of its soluble form; therefore, such interaction could not be excluded. Second, it was suggested that fibrin degradation products could bridge leukocytes to the endothelium via their interaction with endothelial VE-cadherin and leukocyte receptor CD11c, also known as the integrin αX subunit, thus promoting leukocyte transmigration [14]. In particular, the leukocyte migrating activity was attributed to the fibrin degradation product, fragment E_1 [14,15]. However, the E_1 fragment exists only as a part of the D-D:E_1 complex, in which knob ‘A’ (the αGly17-Pro18-Arg19 sequence), the active binding site of E_1, is inaccessible for CD11c, which makes the E_1-mediated intercellular interaction unlikely, unless some other receptor(s) or portions of E_1 are involved as alternative binding sites. The third mechanism of fibrin(ogen)-mediated leukocyte transmigration proposed earlier by the authors of the present study involves fibrin whose interaction with VLDLR via the N-terminal portions of fibrin β chains, known as βN-domains, promotes leukocyte transmigration [6]. However, there was no direct experimental evidence that fibrin can stimulate leukocyte transmigration via this mechanism. Furthermore, it was unclear which fibrin species, soluble fibrin, fibrin polymers, or fibrin degradation products, are involved in such stimulation. The current article by Yakovlev and Medved [5] addressed these questions.

The authors performed a comprehensive and through study of the interaction of recombinant soluble VLDLR, which is normally expressed in endothelial cells, with fibrinogen, fibrin, and their recombinant fragments corresponding to the fibrin(ogen) (B)βN-domains. They also studied the effect of fibrinogen, fibrin, and various fibrin-derived species on transendothelial migration of leukocytes. The authors demonstrated that freshly purified monomeric fibrinogen in solution does not bind to VLDLR and has practically no influence on leukocyte transmigration. However, fibrinogen became highly reactive towards soluble VLDLR either in the adsorbed state or upon conversion to fibrin, implying that the VLDLR-binding site(s) is exposed due to conformational transitions. The study also revealed that the D-D:E_1 complex, high molecular mass fibrin degradation products, soluble fibrin, as well as insoluble fibrin polymers deposited on the endothelium (endothelium-anchored fibrin clots), promote leukocyte transmigration in a VLDLR-dependent manner. These findings provide insights into the molecular and sub-molecular mechanisms underlying the transendothelial migration of leukocytes in thrombotic inflammation and show that it is mediated mainly by the fibrin-VLDLR interaction. Among these findings, the most important one is that endothelium-anchored fibrin clots promote leukocyte transmigration since it establishes an important link between thrombosis and the recruitment of leukocytes to sites of inflammation. This link is demonstrated by a diagram in Fig. 1 providing a summarized mechanistic explanation for the VLDLR-dependent transendothelial migration of leukocytes induced by a fibrin clot deposited on the endothelium, which follows from the article by Yakovlev and Medved [5]. Thus, the results presented in this article certainly have a remarkable (patho)physiological significance because they shed light on clinically and biologically important pathogenic processes underlying many diseases and pathological conditions.

There are a few additional notable points that could be inferred from the article by Yakovlev and Medved [5]. First, this work affirms that a strong mechanistic interplay between inflammation and thrombosis is bidirectional. In other words, it shows that not only local inflammation can enhance hemostatic and thrombotic processes by amplifying clot initiation and limiting fibrinolysis [16], but that fibrin formation and deposition on

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